REMARKS

This amendment is responsive to the non-final Office Action of October 1, 2007. Reconsideration and allowance of claims 1-18 and 22-29 is requested.

Status of the Claims

Claims 1-18 and 22-29 are pending.

Claims 2-4 and 14 stand withdrawn.

Claims 19-21 were previously cancelled, without prejudice.

The Office Action

Claims 2-4 and 14 stand withdrawn.

Claims 1, 5-13, 15-18, and 22-29 stand rejected under 35 U.S.C. §103(a) as being unpatentable over a combination of:

Prusiner, Novel Proteinaceous Infectious Particles Cause Scrapie, Science. 216(9):136-144 (1982);

Castle, et al., Effects of Different Methods of Purification on Aggregation of Scrapie Infectivity, J. Gen. Virol., 68, 225-231, (1987);

Nandi, et al., Unusual Property of Prion Protein Unfolding in Neutral Salt Solution, Biochemistry 41:11017-11024 (2002);

Cai, et al., Solvent-Dependent Precipitation of Prion Protein, Biochimica et Biopohysica Acta, 1597:28-35 (2002);

Ernst and Race, Comparative Analysis of Scrapie Agent Inactivation Methods, *J. Virol. Methods*, 41:193-202 (1993); and

U.S. Application Serial No. 10/467,591 to Kritzler, et al. (2002).

The Present Application

Prions are resistant to many conventional treatment processes used for destruction of microorganisms. Their behavior also differs in many cases to that of conventional proteins. In particular, conformational changes in the structure of prions in various treatments results in a β-sheet structure which is highly resistant to degradation.

The present inventors have found that a treatment in which one or more phenols is combined with an inorganic salt, e.g., sodium chloride, can inactivate prions on a body.

The References of Record

The Prusiner Article, "Novel Proteinaceous Infectious Particles Cause Scrapie," documents work that proposes that scrapie agent contains a protein which can be inactivated by chaotropic salts such as guanidinium thiocyanate, and can be inactivated by phenol. Chaotropic agents of those that disrupt molecular structure. The results presented in Table 1 on page 138 indicate that scrapie is stable against treatments with ions, such as Na^{+}, K^{+}, Cl^{-}, and SO_4^{2-}. Table 1 also indicates that the scrapie agent is stable in the presence of a list of detergents. These results are repeated on page 139, left column, where the Article indicates that the agent was stable in various ionic and nonionic detergents.

The Prusiner Article notes that "extraction in phenol, a potential denaturant of protein, under various salt and *p*H conditions destroyed infectivity (page 139, left column). However, as is evident from a review of the reference on which this statement is based (S.B. Prusiner, D.F. Groth, S.P.Cochran, F. Marsiarz, M.P. Mc Kinley, H.M. Martinez, Biochemistry 19: p4883 (1980)) (Abstract, attached), extraction with phenol resulted in a finding of virtually no infectivity even after examining such variables as pH, salt concentration, and predigestion of samples with proteinase K, i.e., the effects of extracting with phenol were considered independent of salt concentration.

Nandi, et al. discloses that the unfolding of cellular prion protein is unaffected by 0.5 molar sodium chloride, as compared to treatment with buffer (FIG. 1, text). Thus one of skill in the art would conclude, based on Nandi, that sodium chloride has no impact on the secondary structure of the prion protein. Also, on page 11020 it is noted that sodium chloride (0.5 M) is without any effect on the thermal stability of the protein fragment. While the authors note that salt solutions have large effects on the structure and properties of proteins, this is based on studies of proteins in general (p. 11021, left hand column), not on prion proteins. They note that unfolding of prion proteins cannot be explained on the basis of these general considerations (p. 11021, right hand column). Further, they acknowledge that the process of unfolding in prion proteins has not been linked with denaturation of the prion protein (page 1102, right hand column). There is a suggestion on page 11022, bottom of right hand column, that the unfolding of the protein may induce PrP^{Sc} and amyloid formation, thus suggesting a potential for <u>increase</u> in infectivity.

Accordingly, the Nandi reference teaches that the behavior of prion proteins

cannot be predicted on the basis of conventional proteins. One skilled in the art, based on Nandi would not be motivated to use an inorganic salt in a composition to treat a prion-infected body.

Cai, et al. reports studies on precipitation of prion protein in various solvents. Precipitation experiments were performed in sodium acetate or sodium phosphate buffers. Sodium chloride and ethyl alcohol were added to reach desired concentrations of 0.05 to 0.025 M and 0-25%, respectively. Salt was found not to effect $PcP^{Sc/RES}$ precipitation in the absence of ethanol, but enhanced the precipitation in the presence of 25% ethanol. The work of Cai demonstrates that the content of the prion residue in the supernatant can be reduced by precipitating the protein. However, this says nothing about the actual infectivity of the prion protein itself, merely its separation from one fraction to another. As noted on page 34, it was only in the presence of ethanol that any effect on precipitation could be determined for salt.

The Ernst and Race reference discloses treating a scrapie-infected hamster brain homogenate with LpH. As mentioned in the Ernst and Race article, LpH is an aqueous acid phenolic disinfectant which contains o-benzyl-p-chlorophenol at 6.1%, as well as p-tertiary amylphenol at 3%, and phenylphenol at 0.5%.

Kritzler, et al. discloses methods for treating a surface suspension or solution contaminated with prion protein with enzymes. In paragraph 41, Kritzler discloses that certain surfactants tend to bind to proteins and initiate unfolding of their tertiary structure. In paragraph 42 it is noted that inorganic salts can induce conformational transitions in proteins. These paragraphs detail the understanding about proteins in general and not about prion proteins. It can be seen from Table 1 that these general assumptions do not apply to prions (as represented by models of proteins such as bovine albumin with high globulin content).

The Castle reference describes the generation of detergent insoluble residues of scrapie infected tissue by various processes. At one stage in the processes described, pelletized residues are resuspended in a salt solution (e.g., 10% NaCl). The results shown in Table 1 show the infectivity of the tissues before and after processing. The article concludes that the processes were effective for aggregating the infectious prion proteins but that the infectivity remained high (Abstract). This, in fact, is the object of Castle.

The Claims Distinguish Patentably Over the References of Record

Claim 1 calls for a method of treating a body which is contaminated with prions. The method includes contacting the body with a composition comprising a phenol and a soluble inorganic salt to inactivate prions on the body.

The references cited, alone or in combination, do not suggest such a method.

Prusiner teaches that while scrapie agent is inactivated in chaotropic salts, such as guadinium thiocyanate, it is stable in inorganic ions such as sodium and chloride (Table 1 and page 138, right hand col.). Further, Prusiner teaches that the effect of phenol extraction on infectivity is independent of various salt and pH conditions (page 139, left hand column and reference 24). There is, however, no indication that Prusiner is referring to inorganic salts in this discussion. Accordingly, one of skill in the art would not be motivated to treat a body contaminated with prions with a composition comprising phenol and inorganic salt in view of Prusiner.

The Castle reference describes the generation of detergent insoluble residues of scrapie infected tissue by various processes. Castel uses relatively high salt concentrations (e.g., 10% NaCl) to resuspend pelletized residues. This process does not result in a decrease in infectivity. The results shown in Table 1 show the infectivity of the tissues before and after processing. The article concludes that the processes were effective for aggregating the infectious prion proteins but that the infectivity remained high (Abstract). This, in fact, is the object of Castle- to retain infectivity for further study. Accordingly, Castle teaches against there being any benefit by treatment of Prusiner's PrP 27-30 with an inorganic salt. One of ordinary skill in the art would conclude that any conformational changes which may be wrought by the salt of Castle would not lead to denaturation of the prions and would have no effect on the infectivity of the prions.

The remaining references do not solve the deficiencies of Prusiner and Castle.

Nandi, et al. discloses the unfolding of cellular prion protein and its refolding to the scrapie isoform. Nandi studied the effects of the various concentrations of sodium sulfate on the CD (circular dichroism) spectra of mouse prion protein, as described on page 11018 and shown in Figure 1. In the discussion which starts at the bottom of the right-hand column on page 11020 of Nandi, the authors note that salt solutions have large effects on the structure and properties of proteins. These statements, however, clearly refer to proteins, in general, not to prions, as evident

from the following discussion.

Moreover, Nandi notes that the process of unfolding in prion proteins has not been equated to denaturation (page 11022, right hand paragraph). Indeed, as noted at the bottom of page 11022, right hand column, transition of cellular prion protein to the scrapie isoform is associated with prion unfolding. The authors propose that unfolding of a protein molecule allows intermolecular association through non-covalent interaction would lead to oligomerization and subsequent polymerization to amyloid.

Cai, et al. reports studies on the precipitation of prion protein. Precipitation experiments were performed in sodium acetate or sodium phosphate buffers. Sodium chloride was found not to affect $PcP^{Sc/RES}$ precipitation in the absence of ethanol, but enhanced the precipitation in the presence of 25% ethanol. The work of Cai demonstrates that the content of the prion residue in the supernatant can be reduced by precipitating the protein. However, this says nothing about the actual infectivity of the prion protein itself, merely its separation from one fraction to another. As noted on page 34, it was only in the presence of ethanol that any effect on precipitation could be determined for salt. Thus, Cai provides no motivation for using salt in combination with phenol for treatment of a prion infected body.

Ernst & Race (1993) discloses treating a scrapie-infected hamster brain homogenate with LpH. There is no suggestion in this reference that the composition include a soluble inorganic salt.

Kritzler, et al. discloses methods for treating a surface suspension or solution contaminated with prion protein with enzymes. In paragraph 0041, Kritzler discloses that certain surfactants tend to bind to proteins and initiate unfolding of their tertiary structure. In paragraph 0042 it is noted that inorganic salts can induce conformational transitions in proteins. These paragraphs detail the understanding about proteins in general and not about prion proteins. Further, as evident from Nandi, conformational changes cannot be assumed to equate with denaturation, but may lead to a conformational change to an infective form. In sum, the references alone or in combination, do not suggest a method for the treatment of a body which is contaminated with prions salts which includes contacting the body with a composition comprising a phenol and a soluble inorganic salt, such as sodium chloride, to inactivate prions on the body.

The present inventors have found that an inorganic salt, used in combination

with one or more phenols, improves the effectiveness of the phenol, especially at low pH. This is believed to be due, at least in part, to the effects on the phenol solubility. This is not taught or suggested by the references.

Accordingly, it is submitted that claim 1 and claims 2-9, 14-16, 18, 22, and 25-28 dependent therefrom are patentable over the cited references.

Claim 11 calls for a method of treating a body which is contaminated with prions which includes contacting the body with a composition comprising a phenol and a soluble inorganic salt to inactivate prions on the body, the soluble inorganic salt including sodium chloride.

The references of record do not suggest such a method. In addition to the comments noted above, sodium and chloride ions are taught by Prusiner (Table 1) to be inactive against scrapie agent. There is no suggestion that in the tests using various salts with phenols, that sodium chloride was among the salts tested. Further, Castle teaches that salt concentrations of about 10% had no effect on prion infectivity. Nandi found no effect of salt over and above that of a buffer. On page 11021, left-hand column, it is noted that the chloride ion in the concentration range of 0.1 to 0.7 M has little effect on protein stability. Ernst and Race do not teach inorganic salts. Krizler does not suggest that adding an inorganic salt may induce conformational changes of the type which reduce infectivity.

Accordingly, it is submitted that claim 11, and claims 12 and 17 dependent therefrom, are patentable over the cited references.

Claim 13 calls for a method of treating a body which is contaminated with prions, including contacting the body with a composition comprising a phenol to inactivate prions on the body. The phenol includes *o*-phenylphenol and *o*-benzyl-*p*-chlorophenol in a solution that includes brine.

The references do not suggest such a method. None of the references, with the exception of Ernst and Race, suggests treatment with phenol that includes *o*-phenylphenol and *o*-benzyl-*p*-chlorophenol. There is no suggestion in Ernst and Race that such phenols be used in combination with brine. Moreover, as demonstrated in FIGURE 3F of Cai, salt had no effect on precipitation in an acid solution. Castle teaches that 10% salt has no effect on prion infectivity. Thus, one of ordinary skill in the art would not expect brine to have any effect on an acidic phenol such as *o*-phenylphenol and *o*-benzyl-*p*-chlorophenol.

Accordingly, it is submitted that claim 13 distinguishes patentably over the

references of record.

Claim 23 calls for a method of treating a body which is contaminated with prions that includes contacting the body with a composition comprising at least one phenol, the composition comprising a phenol concentration of at least 0.005M and an inorganic salt which is present at a concentration of at least 2% by weight, the phenol including at least one of the group consisting of *p*-chloro-*m*-xylenol; thymol; triclosan; 4-chloro, 3-methylphenol; pentachlorophenol; hexachlorophene; 2,2-methyl-bis(4-chlorophenol); *p*-phenylphenol; 2,3-dimethylphenol; 3,5-dimethoxyphenol; 2,6-dimethoxyphenol; *o*-phenylphenol; *p*-tertiary-amylphenol; *o*-benzyl-*p*-chlorophenol; *p*-chloro, *m*-cresol; *o*-cresol; p-cresol; 2,2-methylenebis(*p*-chlorophenol); 3,4-dihydroxybenzoic acid; *p*-hydroxybenzoic acid; caffeic acid; protocatechuic acid; *p*-nitrophenol; 3-phenolphenol; 2,3-dimethoxyphenol; 2,2-methoxy-bis(4-chloro-phenol); and para-phenylphenol.

The references of record do not suggest treating a body with one or more of the above-mentioned phenols and an inorganic salt at a concentration of at least 2%. Prusiner teaches that the activity of phenol is independent of salt concentration. Castle teaches that 10% salt had no effect on infectivity. The remaining references do not suggest that inorganic salt should be used in combination with these phenols.

Accordingly, it is submitted that claim 23 and claim 24 dependent therefrom distinguish patentably and unobviously over the references of record.

Claim 29 calls for a method of treating a body which is contaminated with prions. The method includes contacting the body with a composition to inactivate prions on the body. The composition includes a phenol, a cosolvent, water, and a surfactant selected from the group consisting of sulphonic acids, sulfonates, and combinations thereof.

Prusiner discloses in Table 1 that the scrapie agent is stable in the presence of a list of detergents. These results are repeated on page 139, left column, where the Article indicates that the agent was stable in various ionic and nonionic detergents. In paragraph 0041, Kritzler discloses that certain surfactants tend to bind to proteins and initiate unfolding of their tertiary structure. This paragraph, however, details the understanding about proteins in general and not about prion proteins. Further, as evident from Nandi, conformational changes cannot be assumed to equate with denaturation, but may lead to a conformational change to an infective form. The Castle reference describes the generation of detergent insoluble residues of scrapie

infected tissue by various processes. There is no suggestion that detergents affect the infectivity or that they should be used in combination with phenols.

Thus, it would not be obvious, in view of the cited references, to contact a body with a composition which includes a phenol, a cosolvent, water, and a surfactant selected from the group consisting of sulphonic acids, sulfonates, and combinations thereof.

Accordingly, it is submitted that claim 29 and claim 10 dependent therefrom distinguish over the references of record.

CONCLUSION

For the reasons set forth above, it is submitted that claims 1-18 and 22-29 distinguish patentably over the references of record and meet all statutory requirements. An early allowance of all pending claims is requested.

In the event the Examiner considers personal contact advantageous to the disposition of this case, she is requested to telephone the undersigned at (216) 861-5582.

Respectfully submitted,

FAY SHARPE LLP

Thomas E. Kocovsky, Jr., Reg. No. 28,383
Ann M. Skerry, Reg. No. 45,655
1100 Superior Avenue
Seventh Floor
Cleveland, OH 44114-2579
(216) 861-5582

N:\MEDZ\201304\TLL0001849V001.doc